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# DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

## Food and Drug Administration

■

# PROPOSED MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

## DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

### Food and Drug Administration

### [ 21 CFR Part 606 ]

### BIOLOGICAL PRODUCTS

### Current Good Manufacturing Practice for Blood and Blood Components

Human blood is a priceless natural resource. Blood transfusion and other blood product therapy is the most developed and widely utilized form of human tissue transplant. It is estimated that over nine million units of whole blood for transfusion were collected in this country last year. In addition, approximately two million liters of plasma are processed annually in the manufacture of blood products.

Although blood is often a life-saving drug, hepatitis, a serious post-transfusion disease transmitted to a recipient by the blood of the donor, has been and continues to be a source of dangerous infection to human beings who receive blood and blood component therapy. Approximately 3,000 deaths and more than 20,000 overt cases of illness have been estimated to have been caused by the transfusion of hepatitis-carrying blood in this country annually. Moreover, many more unapparent (subclinical) cases of hepatitis infection, thought to outnumber overt cases by a factor of at least five to one, are caused by blood transfusion. These undetected cases constitute a particularly dangerous public health hazard since infected persons may unknowingly transmit the disease to others. The great dangers existing in blood therapy make abundantly clear the critical need for the highest standards in collecting, processing, storing and distributing of blood to provide the most complete assurance of consistently high quality. Therefore, the Commissioner of Food and Drugs is hereby publishing this notice of proposed rulemaking for current good manufacturing practices (GMP) for blood and blood components.

The promulgation of standards for these biological drugs is part of an existing effort to increase the quality of blood related health care in this country. Pursuant to the findings of a special Task Force in Blood Banking, the Secretary of Health, Education, and Welfare has established a comprehensive National Blood Policy. One of the fundamental methods prescribed by the Secretary to implement the policy is to "employ the full regulatory authorities now vested in the Federal Government * * * for the purpose of assuring uniform adherence to the highest attainable standards of practice in blood banking, including plasmapheresis and plasma fractionation." On January 31, 1973, the Commissioner of Food and Drugs published in the FEDERAL REGISTER (38 FR 2965) a regulation requiring the registration of all blood banks and other firms collecting, manufacturing, preparing, or processing human blood or blood products pursuant to section 510 of the Federal Food, Drug, and Cosmetic Act. At that time, the Commissioner announced that information derived from blood bank registration would be used in implementing necessary standards for improvement of the nation's blood system and that uniform national regulation may be required.

*A. Blood and blood components in interstate commerce.* Blood and blood components are biological products subject to regulation pursuant to the Public Health Service Act (42 U.S.C. 262) and are drugs as defined in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)(1)).

Blood and blood components are used in the diagnosis, prevention, treatment and cure of disease in man and thus come directly within the definition of a drug as set forth in section 201(g)(1)(B) of the Federal Food, Drug, and Cosmetic Act. Blood is also a drug as defined by section 201(g)(1)(A) of the act since blood is recognized in the current edition of the official United States Pharmacopeia. Every Federal court which has considered the classification of blood has held that blood is a drug within the meaning of the Federal Food, Drug, and Cosmetic Act. United States v. Calise, 217 F. Supp. 705 (S.D. N.Y., 1962); United States v. An article of drug * * * Bacto-Unidisk, 392 F.2d 21 (C.A. 6, 1968), reversed on other grounds 394 U.S. 784 (1969); Blank v. United States, 400 F.2d 302 (C.A. 5, 1968) where the Court held that blood was a misbranded drug but was not a biologic within the meaning of the Public Health Service Act as then written. Congress subsequently amended the biologics law.

Since blood and blood components are drugs, they must meet all statutory requirements of the Federal Food, Drug, and Cosmetic Act and are subject to the full extent of regulation pursuant to all provisions of the act. The jurisdiction of the act is not limited to situations where the drug itself has been or is to be introduced into interstate commerce. Consistent with section 201(g)(1)(D) of the act, if one of a drug's essential components has moved in interstate commerce then the entire drug is subject to the requirements of the act and the FDA may regulate the final drug product. United States v. 40 Cases * * * Pinocchio Brand * * * Pure Olive Oil, 289 F. 2d 343 (C.A. 2, 1961), cert. den. 368 U.S. 831; United States v. 39 Cases * * * Michigan Brand Korleen Tablets, 192 F. Supp. 51 (E.D. Mich., 1961), aff'd sub nom. United States v. Detroit Vital Foods, 330 F. 2d 78 (C.A. 6, 1964), cert. den. 379 U.S. 832; Palmer v. United States, 340 F. 2d 48 (C.A. 5, 1964), cert. den. 382 U.S. 903. If a drug or any one of its essential components has moved in interstate commerce, it is adulterated within the meaning of section 501(a)(2)(B) of the act unless it has been manufactured in conformity with current good manufacturing practice to assure that it is safe and has the quality and purity it purports in its labeling to possess. This provision of the law, as well as the general regulations promulgated thereunder (21 CFR Part 133), are fully applicable to blood and blood components. See 21 CFR 133.300(b). In addition to the general good manufacturing practice regulations for all drugs, the Commissioner may promulgate specific regulations for classes of drugs, such as blood, to emphasize the specific application of the general GMP principles to such drugs.

All blood and blood components which are offered for sale in interstate commerce are also subject to section 351 of the Public Health Service Act (42 U.S.C. 262). All manufacturers must have a license which has been issued upon a showing that the manufacturing establishment and its products meet all applicable standards, prescribed in the biologics regulations, designed to insure the continued safety, purity, and potency of the blood.

Pursuant to section 351(d) of the Public Health Service Act, regulations have been promulgated to assure proper manufacturing procedures, testing, and labeling for many biological products including licensed blood products such as Whole Blood (Human), Red Blood Cells (Human) and Source Plasma (Human).

It is clear that these provisions of the Public Health Service Act specifically authorize the promulgation of good manufacturing practice regulations for all licensed blood, that is, blood to be offered for sale in interstate commerce.

*B. Blood and blood components in intrastate commerce.* It is imperative that blood and its components be collected, processed, and stored to minimize the dangers of the spread of hepatitis in blood based therapy. This is a major impetus to promulgate current good manufacturing practice regulations for blood banking. Adherence to basic collection and manufacturing procedures builds quality control into the production system itself and thus significantly promotes this purpose.

Pursuant to section 361 of the Public Health Service Act (42 U.S.C. 264) and under authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs is authorized to promulgate regulations for any measures which, in his judgment, may be necessary to prevent the introduction, transmission, or spread of blood related communicable disease from one state to another. This authority is designed to eliminate the introduction of communicable disease, such as hepatitis, from one state to another. Of necessity, therefore, this authority must be exercised upon the disease causing substance within the state where it is collected, manufactured, or otherwise found. Thus, the Commissioner may promulgate current good manufacturing practice regulations for intrastate blood banking, pursuant to the act, as hepatitis is a communicable disease. Without proper controls, it is likely to spread on an interstate basis. Human blood is a significant source of hepatitis and other communicable diseases, and, if not collected, processed and distributed under appropriate standards, may contaminate the product. Approximately ten states have inspection or licensing provisions with respect to the collection and processing of blood and blood components. The Commissioner

finds these programs are inadequate to keep blood containing hepatitis virus from the channels of interstate commerce.

The Commissioner concludes that this provision of the Public Health Service Act provides sufficient authority for the promulgation of regulations which are necessary and proper to assure that human blood in interstate commerce is handled so as to be safe for use in man. This authority, together with the requirements under the Federal Food, Drug, and Cosmetic Act, that all channels of commerce be kept free of blood and blood components which are adulterated after the shipment of one or more of their essential components in interstate commerce, mandates that where the public health is concerned, all appropriate regulatory action be pursued.

To utilize the full public protection measures provided in section 361 of the Public Health Service Act, the Commissioner is considering a proposal for specific regulatory procedures to implement his authority to destroy any infected or contaminated articles, wherever found (42 CFR 72.3). These measures will bring this provision of the Public Health Service Act, which the Commissioner is authorized to enforce in the area of blood, into greater conformity with the seizure and condemnation provisions of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 334).

In addition to the authority of section 361 of the Public Health Service Act, the Commissioner notes that the 1962 Drug Amendments, in which both the requirement of current good manufacturing practices and registration of intrastate drug facilities were added to the Federal Food, Drug, and Cosmetic Act, constitute a Congressional finding and declaration that the products of all drug manufacturing establishments "are likely to enter the channels of interstate commerce and directly affect such commerce" (section 301, Pub. L. 87–781). Recognition by Congress of this pragmatic principle of public health further establishes the propriety of uniform standards for blood banking, whether or not a particular establishment directly introduces its blood or blood component into interstate commerce.

The proposed regulations include requirements for complete and truthful labeling for all blood and blood components. Clearly, blood and blood components which move in interstate commerce are subject to all the misbranding provisions of the Federal Food, Drug, and Cosmetic Act, particularly section 502(a), which provides that a drug is misbranded if its labelling is false or misleading in any particular. In addition, section 351(b) of the Public Health Service Act prohibits the false labeling or marking of any package or container of any biological product such as blood. The false labeling provisions of both acts were designed to accomplish substantially the same result and the Commissioner concludes that they should be so interpreted and applied. Significantly, section 351(b) contains no interstate commerce requirement. It applies to all blood whether or not it has moved or is offered for sale in interstate commerce. United States v. Calise, 217 F. Supp. 705 (S.D. N.Y., 1962), and United States v. Steinschreiber, 218 F. Supp. 426 (S.D. N.Y., 1962), 219 F. Supp. 373 (S.D. N.Y, 1963), aff'd 326 F. 2d 759 (C.A. 2, 1964), cert. den. 376 U.S. 962. These statutory provisions authorize standards for labeling for all blood and blood components.

The Commissioner is developing and enforcing a comprehensive regulatory program over a particular class of drugs, namely, blood and blood components. These proposed current good manufacturing practice regulations for both inter- and intrastate blood banking will assure thorough, uniform and efficient enforcement of the law. Such regulations are within the broad Congressional mandate to pursue the high remedial public health purpose of both the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. The Supreme Court has recently reaffirmed that it is "implicit in the regulatory scheme" for the Food and Drug Administration to pursue a comprehensive, industry-wide regulatory program for a particular class of drugs "for the achievement of the agency's ultimate purposes." Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 655 (1973). The regulatory scheme that the Commissioner is pledged to enforce includes not only the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act but any consistent amalgamation of both statutes.

These proposed current good manufacturing practices will apply to all blood banks, transfusion facilities, plasmapheresis centers, compatibility testing establishments and any facility which processes blood or blood components regardless of whether they are intended for interstate or intrastate commerce. The regulations are designed to assure the production of blood and blood components of uniform high quality throughout the nation. Adherence to the prescribed standards by the numerous plasmapheresis centers throughout the country will not only insure the availability of good quality plasma for further manufacturing, but will also protect plasma donors from exploitation.

Pertinent background data and information, as follows, on which the Commissioner relies in proposing this regulation are on public display in the office of the Hearing Clerk, Food and Drug Administration, Room 6–86, 5600 Fishers Lane, Rockville, MD 20852.

1. Perkins, H. A., Schmid, R., and Vyas, G. N. "Hepatitis and Blood Transfusion," Proceedings of a Symposium at the University of California, San Francisco, March 25–26, 1972: Grune and Stratton, Inc., New York, NY.

2. "National Heart and Lung Institute (NHLI) Blood Resource Studies": Department of Health, Education, and Welfare Publication No. (NIH) 73–416, June 30, 1972.

3. "National Blood Policy," Informational Material distributed at Federal Focus on Health Seminar, 1973 (Unpublished).

4. Transcript of the Proceedings: Secretary's (DHEW) Conference on Implementation of the National Blood Policy, September 24, 1973. (Unpublished).

5. Transcript of the Proceedings: Secretary's (DHEW) Conference on Implementation of the National Blood Policy, October 29, 1973 (Unpublished).

6. "Registration of Blood Banks and Other Firms Collecting, Manufacturing, Preparing, or Processing," published in the FEDERAL REGISTER, Vol. 38, No. 20 (38 FR 2965), January 31, 1973.

7. "Standards for Blood Banks and Transfusion Services," American Association of Blood Banks, Washington, DC, 6th Ed. 1971–72, 20th Century Press, Chicago, IL.

8. "Post-transfusion Hepatitis (Cases, Deaths, and Costs)," Conference on the National Blood Policy (DHEW), 1973 (Unpublished).

9. "Summary of State Blood Bank Legislation and Programs," submission of data to the Food and Drug Administration, August 1972 (Unpublished).

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 501, 502, 510, 701, 52 Stat. 1040 as amended, 52 Stat. 1049–1050 as amended by 76 Stat. 780, 76 Stat. 794 as amended, 52 Stat. 1055–1056 as amended, and sec. 301 of Pub. L. 87–781; (21 U.S.C. 321, 351, 352, 360 and note, and 371)), the Public Health Service Act (secs. 351 and 361, 58 Stat. 702 and 703 as amended; (42 U.S.C. 262 and 264)), and the Administrative Procedure Act (secs. 4 and 10, 60 Stat. 238 and 243, as amended; 5 U.S.C. 553, 702, 703, 704) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes that Chapter I of Title 21, Code of Federal Regulations be amended in Subchapter F by adding thereto a new Part 606 as follows:

## PART 606—CURRENT GOOD MANUFACTURING PRACTICES FOR BLOOD AND BLOOD COMPONENTS

### Subpart A—General Provisions

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606.3 Definitions.

### Subpart B—Manufacturing Practices and Procedures

606.10 Facilities.
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606.18 Laboratory controls.
606.19 Personnel.

### Subpart C—Labeling

606.30 Labeling.

### Subpart D—Records and Reports

606.40 Records.
606.41 Distribution procedures and records.
606.45 Adverse reaction file.

AUTHORITY: Secs. 201, 501, 502, 510, 701, 52 Stat. 1040 as amended, 52 Stat. 1049–1050 as amended by 76 Stat. 780, 76 Stat. 794 as amended, 52 Stat. 1055–1056 as amended; 21 U.S.C. 321, 351, 352, 360, 371. Sec. 301, 76 Stat. 793 (21 U.S.C. 360 note). Secs. 351, 361, 58 Stat 702–703 as amended; 42 U.S.C. 262, 264.

## Subpart A—General Provisions

### § 606.3 Definitions.

As used in this part:

(a) "Blood" means whole human blood collected from a single donor and processed either for transfusion or further manufacturing.

(b) "Unit" means the volume of blood or one of its components in a suitable volume of anticoagulant obtained from a single collection of blood from one donor.

(c) "Component" means that part of a single-donor unit of blood separated by physical or mechanical means.

(d) "Plasma for further manufacturing" means that liquid portion of blood separated and used as material to prepare another product.

(e) "Plasmapheresis" means the procedure in which blood is removed from the donor, the plasma separated from the formed elements, and at least the red cells returned to the donor. This process may be immediately repeated, once.

(f) "Facilities" includes any area used for the collection, processing, storage, distribution or compatibility testing of blood and blood components.

(g) "Processing" means any step, including collecting and compatibility testing, in the preparation of a unit of blood or blood components for transfusion or further manufacturing.

(h) "Compatibility testing" (sometimes referred to as "cross-matching") means the in vitro processing performed on a unit of blood or blood components to establish the serological matching of a donor's blood or blood components with that of a potential recipient.

## Subpart B—Manufacturing Practices and Procedures

### § 606.10 Facilities.

The facilities shall be maintained in a clean and orderly manner, and shall be of suitable size, construction, and location to facilitate adequate cleaning, maintenance, and proper operations. The facilities shall:

(a) Provide adequate space for the following when applicable:

(1) Accurate, complete and personalized screening of individuals to determine their suitability to serve as blood donors.

(2) Withdrawal of blood from donors with minimal risk of contamination, or exposure to unrelated activities and equipment.

(3) Quarantine storage of blood or blood components pending completion of tests and of crossmatched bloods.

(4) Storage of finished products ready for distribution.

(5) Storage of products not suitable for use or distribution, or unsuitable reagents prior to discarding to preclude the possibility of their use.

(6) Processing of blood and blood components in work areas arranged in an orderly manner so as to avoid contamination of the product.

(7) The proper performance of all steps in plasmapheresis.

(8) Packaging, labeling and other finishing operations.

(b) Provide adequate lighting and ventilation, and screening of open windows and doors.

(c) Provide adequate handwashing facilities in work areas, and convenient toilet facilities for donors and personnel. Drains shall be of adequate size and, where connected directly to a sewer, shall be equipped with traps to prevent backsiphonage.

(d) Provide for safe and sanitary disposal of trash and items used during the processing of blood and blood components.

### § 606.11 Equipment.

Equipment used for the processing, storage, and distribution, of blood and blood components, shall be maintained in a clean and orderly manner, and shall be located so as to facilitate cleaning and maintenance. The equipment shall be calibrated or tested on a regularly scheduled basis to determine that it is performing within the range of accuracy for which it was designed, and within the official requirements. Equipment which is employed for the sterilization of materials used in processing procedures shall be designed, maintained and utilized so as to insure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 121.5° C. maintained for 20 minutes by saturated steam or by an attained temperature of 170° C. maintained for two hours with dry heat.

### § 606.12 Materials.

All materials used in the processing, storage and distribution of blood and blood components shall be stored and handled in a safe, sanitary, and orderly manner.

(a) All surfaces that come in contact with blood and blood components intended for transfusion shall be sterile, pyrogen-free, and shall not interact with the products in such a manner as to have an adverse effect upon the safety, purity, potency, or effectiveness of the product. All final containers and closures for blood and blood components not intended for transfusion shall be clean and free of surface solids and other contaminants and shall be made of material which will not interact with the contents in such a manner as to have an adverse effect upon the safety, purity, potency, or effectiveness of the product.

(b) Each blood collecting container, and its satellite container, if any, shall be examined visually for damage or evidence of contamination prior to its use. Such examination shall include inspection for breakage of seals when indicated, and discoloration. Where any defect is observed, the container shall not be used.

(c) Representative samples of solutions or reagents liable to contamination or to changes in concentration shall be tested on a regularly scheduled basis by a method designed to determine their freedom from bacteria and/or their strength in order to assure conformance with applicable specifications.

(d) Appropriate records for the primary materials used in processing shall be maintained and shall include:

(1) The identity of the material, name of the supplier (manufacturer), the lot number, the expiration date, and the date of receipt.

(2) The relation of lot numbers of materials used to specific lots or units of the final product.

(3) Examinations and tests performed on the materials, including rejected materials and their disposition.

(e) Processing materials prepared at the facilities shall be tested for strength or potency where appropriate on a regularly scheduled basis. For any materials which require sterilization, records identifying the date, temperature, time and mode of sterilization shall be maintained and such records shall relate the materials to particular units of final product.

(f) Materials used in processing shall be stored in such a manner that the oldest is used first.

(g) Materials used in processing shall be used in a manner consistent with instructions provided by the manufacturer.

(h) Items that are required to be sterile and come in contact with blood should be disposable wherever possible.

### § 606.15 Standard operating procedures.

(a) In all instances, except clinical investigations, standard operating procedures must comply with the Food and Drug Administration's published additional standards in Part 640 of this chapter for the product(s) being processed.

(b) Written standard operating procedures shall be maintained for all steps to be followed in the processing, storage and distribution of blood and blood components. Such procedures shall be available to the personnel for use in the areas where the procedures are performed unless this is impractical. The written operating procedures shall include, but are not limited to, descriptions of the following when applicable:

(1) Criteria used to determine donor suitability including acceptable medical history criteria.

(2) Methods of performing donor qualifying tests and measurements, including minimum and maximum values for a test or procedure when a factor in determining acceptability.

(3) Solutions and method used to prepare the site of phlebotomy to give maximum assurance of a sterile container of blood.

(4) Method of accurately relating product(s) to donor.

(5) Blood collection procedure including in-process precautions taken to accurately measure quantity of blood removed from donor.

(6) Methods of component preparation, including any time restrictions for specific steps in processing.

(7) All tests performed on blood and blood components, including testing for

hepatitis B antigen using licensed reagents.

(8) Compatibility testing, when applicable, including precautions to be taken to accurately identify recipient blood samples and cross-matched donor units.

(9) Storage temperatures and methods of controlling storage temperatures for all blood products and reagents.

(10) Length of expiration dates assigned for all final products.

(11) Criteria for determining that returned blood is suitable for reissue.

(12) Distribution records including the procedures used for relating a unit of blood or blood component from the donor to its final disposition.

(13) Quality control procedures for processing materials or reagents.

(14) Schedules and procedures for equipment maintenance and calibration.

(15) Labeling procedures, including safeguards to avoid labeling mixups.

(16) Procedure of plasmapheresis, if to be performed, including precautions to be taken to insure reinfusion of the donor's own cells.

(c) All records, maintained pursuant to these regulations, shall be reviewed prior to the release or distribution of a lot or unit of final product. A thorough investigation of any unexplained discrepancy or the failure of a lot or unit to meet any of its specifications shall be undertaken. A written record of the investigation shall be made and shall include the conclusions and followup.

(d) In addition to the requirements of this subpart and in conformity with this section, any facility may utilize existing standard operating procedures such as the manuals of the following organizations, as long as such specific procedures are consistent with and at least as stringent as the requirements contained in this part.

(1) American Association of Blood Banks.

(2) American National Red Cross.

(3) Other organizations or individual blood banks, subject to approval by the Director, Bureau of Biologics.

### § 606.16 Plasmapheresis.

(a) Plasmapheresis may be used as the method of collecting blood for the preparation of components for injection or plasma for further manufacturing. Processing of products obtained by plasmapheresis and not subject to the additional standards for Source Plasma (Human) shall include at a minimum the following:

(1) A written informed donor consent.

(2) An initial medical examination of the donor no more than one week prior to first donation.

(3) A donor eligibility requirement of a total serum protein of no less than 6.0 grams per 100 milliliters of serum, and a weight of at least 110 pounds.

(4) A serum protein electrophoresis or quantitative immunodiffusion test for immunoglobulins performed on a sample of donor's blood taken at the time of the first donation and every 4 months thereafter.

(5) Medical supervision of all aspects of the procedure, including a personal review of accumulated laboratory data, immunization schedules, and collection records at 4-month intervals to determine continuing suitability of the donor.

(b) *Blood containers.* Blood containers and donor sets shall be pyrogen-free, sterile and identified by lot number. The amount of anticoagulant required for the quantity of blood to be collected shall be in the blood container when it is sterilized.

(c) *The anticoagulant solution.* The anticoagulant solution shall be sterile and pyrogen-free. One of the following formulae shall be used in the indicated volumes:

(1) *Anticoagulant acid citrate dextrose solution (ACD).*

| | |
|---|---|
| Tri-sodium citrate ($Na_3C_6H_5O_7.2H_2O$) | 22.0 grams. |
| Citric acid ($C_6H_8O_7.H_2O$) | 8.0 grams. |
| Dextrose ($C_6H_{12}O_6.H_2O$) | 24.5 grams. |
| Water for injection (U.S.P.) to make. | 1,000 milliliters. |
| Volume per 100 milliliters blood. | 15 milliliters. |

(2) *Anticoagulant citrate phosphate dextrose solution (CPD).*

| | |
|---|---|
| Tri-sodium citrate ($Na_3C_6H_5O_7.2H_2O$). | 26.3 grams |
| Citric acid ($C_6H_8O_7.H_2O$) | 3.27 grams |
| Dextrose ($C_6H_{12}O_6.H_2O$) | 25.5 grams |
| Monobasic sodium phosphate ($NaH_2PO_4.H_2O$) | 2.22 grams |
| Water for injection (U.S.P.) to make. | 1,000 milliliters |
| Volume per 100 milliliters blood. | 14 milliliters |

(3) *Anticoagulant sodium citrate solution.*

| | |
|---|---|
| Tri-sodium citrate ($Na_3C_6H_5O_7.2H_2O$). | 40.0 grams |
| Water for injection (U.S.P.) to make. | 1,000 milliliters |
| Volume per 100 milliliters blood. | 10 milliliters |

(d) The following limits of whole blood withdrawal, not including anticoagulant, shall be enforced:

(1) Donors weighing less than 175 pounds: 500 milliliters may be removed at one time, but no more than 1,000 milliliters in any 48-hour period, and no more than 2,000 milliliters within a 7-day period.

(2) Donors weighing 175 pounds or greater: 600 milliliters may be removed at one time, but no more than 1,200 milliliters in any 48-hour period, and no more than 2,400 milliliters within a 7-day period.

(e) The plasma shall be separated from the red blood cells immediately after collection, and the maximum feasible volume of red blood cells shall be returned to the donor before another unit is collected.

(f) The following exceptions to whole blood donor requirements shall be permitted, provided that the final product is plasma for further manufacturing into reagents or chemically separated products.

(1) Blood may be collected from a donor who has received an immunizing antigen derived from human blood within the preceding 6 months provided that the antigen is a product licensed for such purpose or one specifically approved by the Director, Bureau of Biologics, Food and Drug Administration.

(2) The serological test for syphilis shall be performed initially and at 4-month intervals. A donor with a reactive serologic test for syphilis shall not be plasmapheresed again until his serum is non-reactive to a serologic test for syphilis, except for those donors being plasmapheresed for plasma to be used for further manufacturing into a control serum for the serologic test for syphilis.

(3) A history of malaria or suppressive therapy shall not disqualify a donor.

### § 606.17 Compatibility testing.

Compatibility testing, if performed, shall be done in an area set aside for such purpose and not used for unrelated activities. The compatibility testing standard operating procedures shall include the following:

(a) A method of collecting and identifying recipient's blood samples to insure positive identification.

(b) The use of fresh serum samples less than 48 hours old for all compatibility testing.

(c) The testing of the donor's cells with the recipient's serum (major crossmatch) by a method that will demonstrate both agglutinating and coating antibodies, which shall include the antiglobulin method.

(d) A provision that if the unit of donor's blood has not been screened by the antiglobulin method and other tests to demonstrate both agglutinating and coating antibodies, the compatibility test shall include testing the recipient's cells with the donor's serum (minor crossmatch).

(e) A modified, safe procedure to expedite transfusions in life-threatening emergencies. Records of all such incidents shall be maintained, including complete documentation justifying the emergency action, which shall be signed by the physician requesting the modified procedure.

### § 606.18 Laboratory controls.

Laboratory control procedures shall include the establishment of scientifically sound and appropriate specifications, standards and test procedures to assure that blood and blood components are safe, pure, potent and effective. Laboratory control procedures shall include:

(a) Adequate provisions for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and laboratory instruments.

(b) Adequate identification and handling of all test samples so that they are accurately related to the specific unit of product being tested, or to its donor, or to the specific recipient, where applicable.

### § 606.19 Personnel.

The entire operation of a facility at which processing, storage, or distribution of blood and blood components is performed shall be under the direction of a designated, qualified person.

(a) The personnel responsible for processing, storage and distribution of blood and blood components, shall be adequate in number and background of education, training, and experience, including professional training as necessary, or combination thereof, to assure competent performance of their assigned functions, and to insure that the final product has the safety, purity, potency, identity, and efficacy that it purports to possess. All personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the procedures or control operations they perform, the necessary training or experience, and adequate information concerning the application of pertinent provisions of this part to their respective functions.

(b) Persons whose presence can adversely affect the safety and purity of the products, shall be excluded from areas where the processing of blood or blood components is in progress.

### Subpart C—Labeling

**§ 606.30 Labeling.**

Labeling operations shall be physically or spatially separated from other operations in such a manner that will prevent mixups.

(a) The labeling operation shall include the following labeling controls:

(1) The holding of labels upon receipt pending review and proofing against an approved final copy, to assure they are accurate and conform to the approved copy.

(2) The storage of different product labels in such a manner so as to prevent mixups, and to assure that stocks of obsolete labels are destroyed.

(3) All necessary checks in labeling procedures to prevent errors in translating test results to container labels.

(b) All labeling shall be clear and legible and include the following information as well as other specialized additional information as may be required in Part 640 of this chapter for specific products:

(1) The proper name of the product placed in a prominent position.

(2) The name and address of the manufacturer, and if licensed the license number.

(3) The donor or lot number relating the unit to the donor.

(4) The expiration date, including the day and year and, if it is a factor, the hour, or in the case of plasma for further manufacture, the date of collection.

(5) All necessary instructions or precautions for use.

(6) Recommended storage temperature.

(7) Reference to an instruction circular containing dosage information instructions for use, route of administration, contraindications, and other directions, if product is not intended for further manufacturing.

(8) Quantity of product in container.

(9) Quantity of source material, and kind and quantity of anticoagulant.

(10) Additives and cryophylactic agents added to the product, which may still be present.

(11) Results of all tests performed when necessary for safe and effective use.

(12) The statement: "Caution: For Manufacturing Use Only", where applicable.

(13) The kind of immunizing antigen used or the antibody present for products for further manufacturing, when applicable.

### Subpart D—Records and Reports

**§ 606.40 Records.**

(a) Records shall be maintained concurrently with the performance of each significant step in the processing, storage, and distribution, of each unit of blood and blood components, so that all steps can be clearly traced. All records shall be legible, indelible, shall identify the person performing the work, shall include dates of the various entries, shall show test results as well as the interpretation of the results, the expiration date assigned to specific products, and shall be as detailed as necessary to provide a complete history of the work performed.

(b) A donor number must be assigned to each accepted donor that relates the unit of blood collected to that donor, his medical record, any component or blood product from that donor's unit of blood, and to all records describing the history and ultimate disposition of these products.

(c) Records shall be retained for such interval beyond the expiration date as is necessary for the blood or blood component, to facilitate the reporting of any unfavorable clinical reactions. The retention period shall be no less than five years after the records of processing have been completed, or 6 months after the latest expiration date for the individual product, whichever is a later date. When a collection date is used in lieu of an expiration date, i.e., Source Plasma (Human), records of processing shall be retained for 6 months after the latest expiration date for the final product which was manufactured from the source plasma.

(d) A record of individuals determined not suitable as donors shall be available so that subsequent donations will neither be accepted nor distributed during the period of ineligibility.

**§ 606.41 Distribution procedures and records.**

Distribution procedures shall include a system by which the distribution of each unit can be readily determined to facilitate its recall if necessary. Distribution records shall contain the name and address of the consignee, the date and quantity delivered, the lot number of the unit(s), the date of expiration, or the date of collection, whichever is applicable, or for crossmatched blood and blood components, the name of the recipient.

**§ 606.45 Adverse reaction file.**

Records shall be maintained of any reports of complaints of adverse reactions regarding each unit of blood or blood component. A thorough investigation of each reported adverse reaction shall be made. A written report of the investigation, including conclusions and follow up, shall be maintained as part of the record for that lot or unit of final product. When a severe adverse reaction is confirmed, the Director, Bureau of Biologics, shall be notified immediately.

The Commissioner proposes that the effective date of these regulations shall be 30 days after the date of publication of the final order in the FEDERAL REGISTER.

Interested persons may, on or before August 26, 1974, file with the Hearing Clerk, Food and Drug Administration, Room 6–86, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during regular business hours, Monday through Friday.

Dated: May 21, 1974.

A. M. SCHMIDT,
*Commissioner of Food and Drugs.*

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